TACSM Abstract

Nexrutine® mimics Exercise Preservation of Muscle in TRAMP Mice by Decreasing Proteolysis-Inducing Factor

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ABSTRACT

Cachexia is an adverse effect of prostate cancer (PCa) characterized by skeletal muscle loss which significantly impacts mortality and quality of life. Recently, proteolysis-inducing factor (PIF) mediated activation of the ubiquitin proteasome system has been identified as a potential target for treating cachexia. Oncologists encourage nutritional and physical intercession to improve outcomes, however, it is unclear how these interventions impact PIF activity. **PURPOSE:** To test the hypothesis that Nexrutine® (a natural bark extract of the Amur cork tree with anti-inflammatory capabilities) and exercise can independently attenuate muscle loss in a transgenic adenocarcinoma of mouse prostate (TRAMP) model by modulating PIF. **METHODS:** Forty-five, ten-week old male TRAMP mice were randomized to either control (Con), Nexrutine® (Nex; 600 mg/kg pelleted into chow) or exercise (Ex; voluntary wheel running), for up to 20-weeks. Mice were weighed and sacrificed at 4, 8, 12 and 20 weeks at which time gastrocnemius muscle was collected, weighted and frozen until analysis. Intramuscular PIF and ubiquitin (Ub) were quantified using commercially bought ELISA kits. An analysis of variance was conducted using a Tukey's post hoc test with significance set at $p<0.05$. **RESULTS:** Analysis of gastrocnemius mass revealed significance ($F=4.159$, $p=0.02$), with both Nex and Ex treatment groups having greater mass compared to Con ($p<0.05$). Protein concentrations of PIF ($F= 8.633$, $p=0.001$) and Ub ($F=19.55$, $p<0.001$) revealed a significant treatment effect between groups. Specifically, Ex mice had significantly lower concentrations of PIF and Ub compared to Con ($p<0.001$). Time point comparison between groups with respect to Ub concentration revealed significant differences at weeks 4 ($F=32.35$, $p<0.001$) and 8 ($F=16.24$, $p=0.002$), respectively. Post hoc comparisons revealed significantly smaller concentrations of Ub in Ex mice compared to Con mice ($p=0.004$) at both time points. Group comparisons at 20 weeks showed significantly lower concentrations of PIF ($F= 22.85$, $p<0.001$) and Ub ($F=8.295$, $p=0.008$). Specifically, exercise significantly lowered PIF ($p<0.001$) and Ub ($p=0.006$) concentrations compared to Con. Further, Nex lowered PIF concentrations compared to control ($p=0.03$). **CONCLUSION:** Results suggest that Nex can mimic the effects of Ex in preventing muscle loss in TRAMP mice through reduction of PIF and preservation of muscle mass. While exercise reduced downstream Ub, the mechanism by which Nex elicits a protective effects remains unknown.